THE CURATIVE ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF PATIENTS WITH LOCALIZED NON-HODGKIN'S LYMPHOMA*

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ABILITY to achieve complete remission in approximately 70 to 80% of patients with advanced "unfavorable histology" non-Hodgkin's lymphoma with intensive multiagent combination chemotherapy has recently been reported. With follow-up periods up to five years or more, prolonged disease-free survival is projected for approximately half of those achieving complete remission.[1-4] Such success in patients with advanced disease has naturally promoted the recommendation for use of chemotherapy as initial treatment for those with limited disease, a group in whom recurrence occurs in half of those treated by radiation therapy alone.[5,6] Given the long-established precedent for cure of certain patients with localized disease by irradiation with relatively little treatment-associated morbidity, the current success of chemotherapy and its attendant morbidity has forced reevaluation of the role of radiation therapy in patients with lymphoma of "unfavorable" histology.

Reexamination of radiation therapy in patients with "favorable histology" lymphoma has not been precipitated by chemotherapeutic success because no evidence to indicate that sustained control of "favorable histology" lymphoma by cytotoxic drugs exists. Indeed, pressure to establish the role of radiation therapy is based upon the wish to avoid denial of the only currently available conventional potentially curative option in an environment of increasing belief that all patients with "favorable histology" lymphoma have systemic disease and are therefore, by definition, incurable.

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*Presented at a meeting of the Section on Radiology with the New York Roentgen Society at the New York Academy of Medicine held January 20, 1986.

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To define the role of curative radiation therapy in patients with non-Hodgkin's lymphoma, certain tenets of the process by which treatment is selected must also be examined. These include: the results of intensive staging investigation studies that indicate that localized "favorable histology" lymphoma rarely, if ever, exists and hence can rarely be cured by a localized treatment modality; the confidence with which treatment decisions can be based upon cytologic distinctions within disease classification, given that such morphological distinctions are both inherently subjective and subject to substantial inter-reviewer variation; and the confidence with which actuarial projection of current chemotherapeutic success can be accepted as a mature reflection of the true natural history of treated disease.

Consider first the situation with regard to patients with "unfavorable histology" non-Hodgkin's lymphomas.

Conventionally, radiation therapy—a localized treatment modality—has been the favored treatment for patients with localized disease (clinical stage I and II). Experience has defined that such a policy results in a recurrence rate of 50 to 60%, and, given the inadequacies of previous chemotherapy programs, a resulting mortality rate of approximately 50%. Thus, given histology and stage alone, the power of radiation therapy to determine prognosis was equivalent to tossing a coin. Furthermore, prognostication has not been improved by knowledge of localized nodal versus localized extranodal presentation.

In an attempt to rationalize the use of radical irradiation in patients with localized lymphoma, the Princess Margaret Hospital experience with 716 patients who had non-Hodgkin's lymphoma and who were treated between 1967 and 1978 was examined. The median follow-up for all patients was 10 years (range 0.6-206 months). 496 patients were treated by radical irradiation alone. Actuarial overall survival, cause-specific survival (survival analysis using death from disease or treatment as the end point of interest), and relapse-rates were 49%, 54%, and 45% respectively for the whole group (716 patients), and 49%, 58% and 49% respectively for the radically irradiated group (496 patients).[7]

Prognostic factors were examined for the whole group and for patients receiving radical irradiation. In order of importance, the independent prognostic factors in cause-specific survival analysis were tumor bulk, age, stage, and histology as defined by the Rappaport Classification.[8] The definitions of tumor bulk were small (<2.5 cm residuum), medium (2.5-5.0 cm) or

large (>5.0 cm residuum pre-therapy). Age was a continuous variable with a marked worsening in the prognosis for patients more than 60 years of age. Stage of disease was defined as IA, IIA localized (contiguous sites of nodal or extranodal disease), IIA extensive (discontiguous sites of disease), and symptomatic disease stages IB and IIB. Histological categories were subgrouped into diffuse lymphocytic well-differentiated, nodular lymphocytic poorly differentiated, and nodular mixed lymphoma (low grade lymphoma in the Working Formulation),[9] nodular histiocytic, diffuse lymphocytic poorly differentiated and diffuse mixed lymphoma (intermediate grade) and diffuse histiocytic and diffuse undifferentiated lymphoma (high grade lymphomas). The major distinction in prognosis was between those histologies encompassed by the low-grade grouping (Working Formulation)[9] and those in the intermediate and high-grade categories, although it must be acknowledged that the survival for patients with nodular histiocytic lymphoma was intermediate between the other prognostic groupings.

Given the clear distinction in survival between the low-grade and intermediate plus high-grade categories, the patient population was distinguished accordingly, and the outcome following radical irradiation was analyzed with reference to tumor bulk, age and stage. The effect of these attributes on relapse-rate following radical radiation is shown in Table I. The actuarial relapse-free rates and causes-specific survival curves are shown in Figures 1*a* and 1*b* for the three prognostic categories defined. Figure 2*a* also illustrates that relapse-rate was not a function of histological subtype within the intermediate plus high-grade categorization. Thus, following radiation therapy only, a subgroup of patients with intermediate and high-grade lymphoma who have an actuarial cause-specific survival of 87% and a relapse-free rate 77% at 10 years of follow-up can be defined according to tumor bulk, age, and stage (Group 1).

Patients in Group 2 had an actuarial cause-specific survival of 55% and a relapse-free rate of 49%, the conventional expectation for patients receiving radiation for stage I and II non-Hodgkin's lymphoma. The cause-specific survival of 10% and a relapse-free rate of 10% clearly indicate the palliative nature of irradiation for patients in Group 3.

How does this translate into management of patients? By reference to this retrospective analysis, the attributes—patient age, stage (degree of localization of disease), and tumor bulk—can discriminate a group of patients with intermediate and high-grade lymphoma who have a cause-specific survival

TABLE I. RELAPSE RATES FOR PATIENTS WITH CLINICAL STAGE I AND II INTERMEDIATE AND HIGH GRADE LYMPHOMA TREATED WITH RADICAL IRRADIATION ACCORDING TO AGE, STAGE, AND TUMOR BULK

Stage	*IA IIA Loc*			*IIA EXT + B*		
Bulk / *Age*	*S*	*M*	*L*	*S*	*M*	*L*
<60	18/78	14/24	17/29	8/15	11/21	10/13
	Group 1		Group 2			
60 - 69	13/34	7/14	7/15	2/4	3/3	8/8
					Group 3	
≥70	14/27	12/21	12/14	3/3	6/6	3/3

No. relapsed/No. patients
S=small, M=medium, L=large, as defined in text
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TABLE II. RELAPSE RATES FOR PATIENTS WITH CLINICAL STAGE I AND II LOW GRADE LYMPHOMA TREATED WITH RADICAL IRRADIATION ACCORDING TO AGE, STAGE, AND TUMOR BULK

Stage	*IA, IIA Loc.*			*IIA Ext. + B*		
Bulk / *Age*	*S*	*M*	*L*	*S*	*M*	*L*
<60	10/47					
	Group 1		18/49			
			Group 2			
60 - 69						
						31/47
>70						Group 3

No. relapsed/No. patients
S=small, M=medium, L=large, as defined in text
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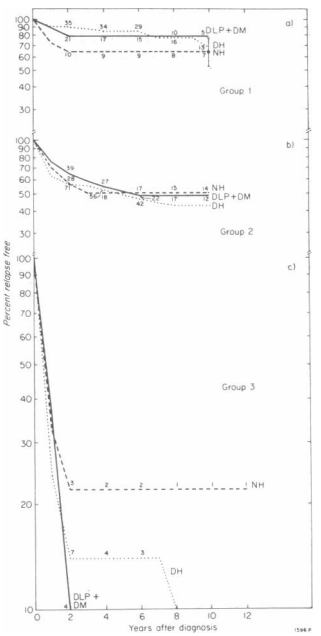

Fig. 1*a*. Actuarial relapse rates for patients with clinical stage I and II non-Hodgkin's lymphoma of intermediate and high grade histologies according to prognostic groups 1, 2, 3 (see Table I for prognostic groups). Relapse-free curves are subcategorized by histologic subgroup in the Rappaport classification. Reproduced with permission from Sutcliffe, S.B., Gospodarowicz, M.K., Bush, R.S., et al.: Role of radiation therapy in localized non-Hodgkin's lymphoma. *Radiother. Oncol. 4*:211-23, 1985.

of 87% at 10 years and a recurrence rate of 23% following radical radiation alone. The same attributes also define those patients in whom the recurrence rate with radiation therapy will be approximately 50% (Group 2). The argument for intensive chemotherapy as an initial component of treatment for such patients can therefore be strongly supported. Can effective chemotherapy improve this situation? Is the radiation necessary? Are we sure that current chemotherapy programs can ensure a 50% cure rate for patients with ostensibly localized lymphoma in the absence of radiation? Is indiscriminate randomization of all patients with localized intermediate and high-grade lymphoma to treatment with radiation or radiation plus chemotherapy desirable when very good and very bad groups can be defined according to outcome following radiation by access to relatively simply-defined prognostic attributes? A randomized study may be more appropriate in patients in our Group 2 category, addressing the benefits of planned chemother-

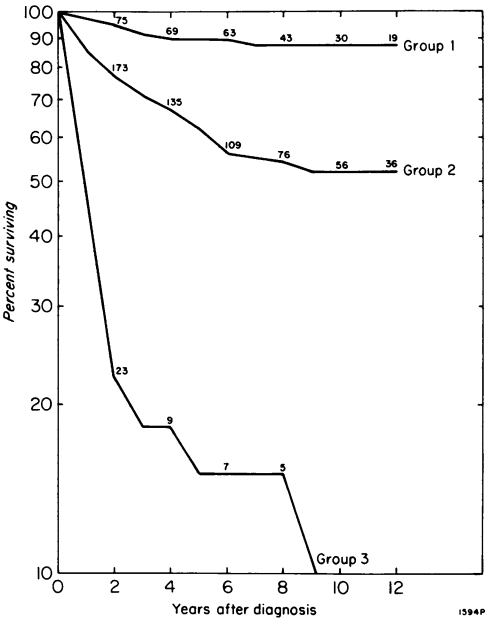

Fig. 1*b*. Actuarial cause-specific survival for patients with clinical stage I and II lymphoma of intermediate and high grade histologies according to prognostic groups 1, 2, and 3 (see Table I). Reproduced with permission from Sutcliffe, S.B., Gospodarowicz, M.K., Bush, R.S., et al.: Role of radiation therapy in localized non-Hodgkin's lymphoma. *Radiother. Oncol.* *4*:211-23, 1985.

apy and irradiation versus chemotherapy following failure after radiation with appropriate reference to survival, relapse-free and morbidity end-points. Two additional factors should also be defined in the selection of radiation therapy for patients with localized intermediate and high-grade lymphomas: are all localized extranodal sites of presentation comparable in their outcome following irradiation? As with all analyses of localized lymphoma, the extranodal sites most commonly seen are gastrointestinal tract lymphomas (predominantly stomach and ileo-cecal origin) and head and neck lymphomas. Other extranodal sites are comparatively much more rare.

In common with other groups, analysis of Princess Margaret Hospital data has established that localized head and neck and gastrointestinal tract lymphomas have a similar, indeed a better prognosis than nodal lymphomas of comparable stage and bulk.[10,11] Certain other extranodal presentations appear to be clearly less favorable, e.g., testis, cerebral, and intraocular lymphoma.[12,13,14] In fact, if all extranodal sites other than localized lymphoma involving mucosa-associated lymphoid tissue (the majority of head and neck

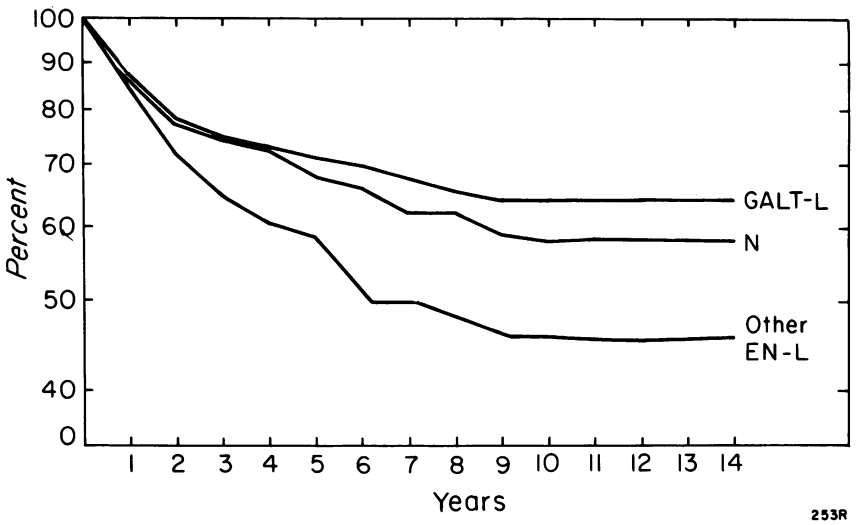

Fig. 2. Actuarial cause-specific survival rates for patients with clinical stage I and II non-Hodgkin's lymphoma. GALT-L refers to lymphoma arising in gut-associated (or mucosa-associated) lymphoid tissue. N refers to nodal lymphoma and E.N.-L. refers to lymphomas arising in extranodal sites other than those associated with gut (or mucosal) associated lymphoid tissue. The survival curves have been adjusted for the effects of the other prognostic variables—age, stage, and tumor bulk. The difference in survival rates between lymphomas arising in gut-associated lymphoid tissue and those arising in other extra-nodal sites is statistically significant ($p=0.017$).

and gastrointestinal tract lymphomas) are aggregated, this variance in prognosis can be represented in both survival (Figure 2) and recurrence-free analysis following radiation therapy.

A more favorable outcome for patients with mucosa-associated lymphoid tissue lymphomas compared with nodal or other extranodal lymphomas is apparent even following adjustment for all other identified prognostic factors (age, stage, and bulk). One potential explanation for this difference may be the ecotaxopathic characteristics of lymphoma cells from mucosa-associated lymphoid-tissues,[15-17] which, by virtue of selective migration properties, favor a greater propensity for localisation of disease in apparently early-stage lymphoma. The converse may be true for lymphomas arising in non-mucosa-associated lymphoid tissue extranodal sites, although definitive proof for such an explanation is lacking and will require a more detailed analysis of failure patterns of non-mucosa-associated lymphoid tissue extranodal lymphomas managed by current investigative and treatment techniques.

Do equivalent histologies within the designation of localized intermediate and high grade lymphoma confer equivalent outcome following radiation therapy?

Analysis by morphological distinction of histologic subtypes in the Princess Margaret Hospital retrospective analysis would suggest equivalent outcome in that no significant differences exist between subtypes according to the Rappaport Classification. However, the analysis is heavily biased in favor of lymphomas of diffuse histiocytic type as opposed to supposedly less aggressive (nodular histiocytic or diffuse poorly-differentiated or mixed lymphoma) or more aggressive lymphomas (lymphoblastic, Burkitt, or undifferentiated non-Burkitt lymphoma).

Is the selection process for irradiation adequate for patients with the very high-grade histologies, e.g., Burkitts, undifferentiated non-Burkitts, and lymphoblastic lymphoma? Should one distinguish lymphomas of T-cell origin from those of B-cell origin? Is grade or proliferative activity, as assessed by cytofluorimetric analysis of cellular DNA-distrubution, a factor of importance? The contribution of these factors as independent determinants of prognosis is not yet available, but may well be important to decision-making with regard to localized versus systemic treatments.

Can the role of radiation therapy be rationalized for patients with apparently localized low-grade lymphoma? Using the prognostic factors—age, degree of localization and tumor bulk—prognostically distinct sub-groups within low-grade localized lymphoma can also be defined (Table II). For patients in Group 1 (<60 years, localized, small bulk) the actuarial cause-specific survival rate was 95% at 10 years with a relapse-free rate of 80% (Figures 3*a* and 3*b*). Both curves become horizontal to the time axis indicating the infrequency of relapse or tumor-related death after five to six years of follow-up. Are these patients cured? Inasmuch as the relapse-free rate approaches zero after six years, one might say that such is the case. It may be more appropriate, however, to state that such favorably selected patients need 15 to 30 years of follow-up to know the true impact of therapy.

Of interest also are the results of radiation therapy in Group 2. Such patients demonstrated an actuarial cause-specific survival of 85% at 10 years and a relapse-free rate of 63%. How selected are patients in Groups 1 and 2 of the low-grade histology population? They comprise 30% of all patients with low-grade lymphoma during the 11-year period of study at Princess Margaret Hospital. If the actuarial relapse-free rate for patients in Groups 1 and 2 exceeds 60%, the potential for prolonged relapse-free survival for

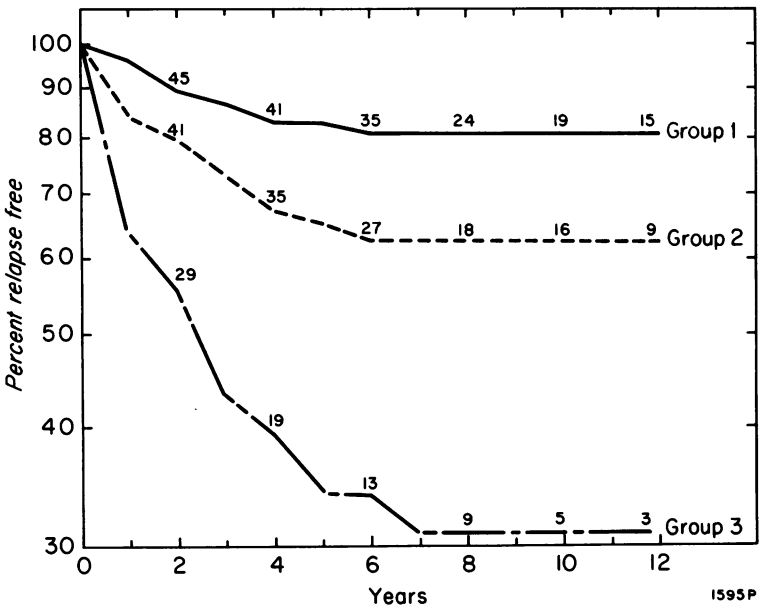

Fig. 3*a*. Actuarial relapse-free rate for patients with clinical stage I and II non-Hodgkin's lymphoma of low grade histology according to prognostic groups 1, 2, and 3 (Table II). Reproduced with permission from Sutcliffe, S.B., Gospodarowicz, M.K., Bush, R.S., et al.: Role of radiation therapy in localized non-Hodgkin's lymphoma. *Radiother. Oncol. 4*:211-23, 1985.

patients with low-grade lymphoma is approximately 20%. How does this figure correlate with studies of intensive investigation of patients with low-grade lymphoma? These studies, employing all staging procedures up to and including staging laparotomy, indicated that only approximately 6% of patients with stage I and II low grade lymphoma had truly localized disease.[18] Why do we seem to have 20% of such patients free of relapse after radiation with a median follow-up period of nine years? There is no ready answer: perhaps even more mature follow-up data are required to define the real rate of relapse, maybe the staging investigations revealed a high rate of false positive examinations, maybe one does not need to treat all occult disease to render patients with localized low-grade lymphoma free from future relapse?

Additional studies may answer these questions, but from a practical viewpoint, is it right to deny radiation therapy to such patients in the belief that localized low-grade lymphoma never occurs, particularly when the treatment

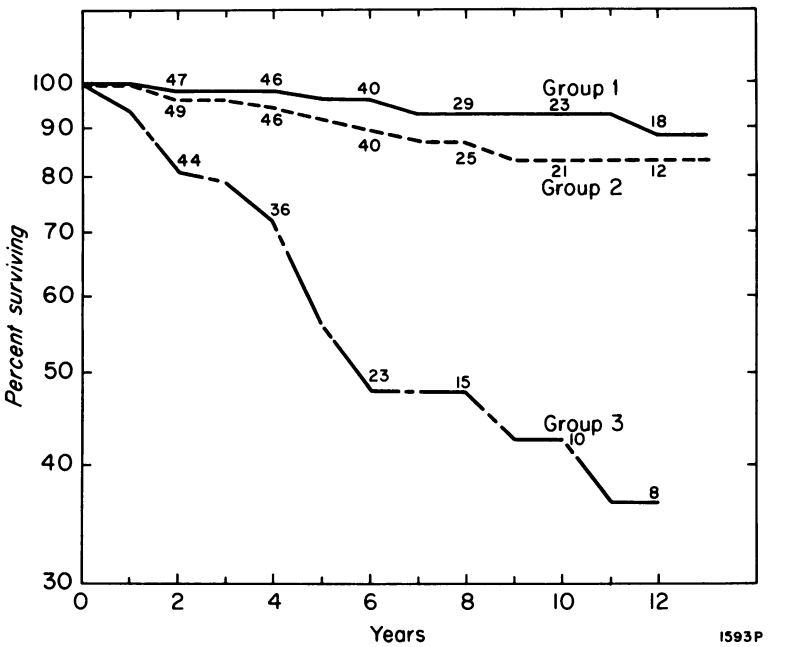

Fig. 3*b*. Actuarial cause-specific survival for patients with clinical stage I and II non-Hodgkin's lymphoma of low grade histology according to prognostic groups 1, 2, and 3 (Table II). Reproduced with permission from Sutcliffe, S.B., Gospodarowicz, M.K., Bush, R.S., et al.: Role of radiation therapy in localized non-Hodgkin's lymphoma. *Radiother. Oncol.* *4*:211-23, 1985.

is in large part without significant morbidity? This position is put forward with reference to the role of radiation therapy in patients with apparently localized low-grade lymphoma. In the absence of any alternative potentially curative therapy, can one deny such patients the possibility of a 10%, or perhaps even 20%, long-term relapse-free status following radiation?

How dependent are management decisions for patients with non-Hodgkins lymphoma upon morphological distinctions within existing histologic classifications? In this retrospective analysis, histological subcategorization within the Rappaport Classification had independent prognostic significance. While patients with localized well-differentiated diffuse lymphocytic lymphoma were included in the analysis, the number was very small. Furthermore, such patients were probably highly selected from a much larger patient population managed without reference to an oncology center. Thus, the major prognostic utility of the histological classification (independent of patient age,

stage, and tumor bulk) was in the distinction of those lymphomas with a nodular architecture, i.e., a clear origin from the germinal follicle, from those with diffuse effacement of the node, i.e., those derived from the germinal follicle but without retention of follicular architecture or those derived from nonfollicular zones of the lymph node. Such prognostic distinction has been repeatedly confirmed in both univariate and multiparameter analysis. Of equal importance, however, was failure of cytological distinction of differentiation to predict relapse or survival following radiation. Accordingly, one might question whether distinctions of poorly differentiated lymphocytic lymphoma from mixed or histiocytic lymphoma are justifiable, given that they describe a dynamic process of transformation which is not only susceptible to individual subjectivity but also to geographic and temporal sample bias. In practice, the distinction of low grade lymphoma from intermediate plus high grade lymphoma would appear quite sufficient to separate those in whom current chemotherapy is palliative (low grade) from those who may be potentially curable by intensive chemotherapy. At an even simpler level, much of this discrimination would be served by "nodular versus diffuse" given the limitations of chemotherapy. Thus, with access to readily attainable patient attributes and without resort to controversial morphological description of lymph node lesions, sound decisions regarding the optimal use of radiation therapy for patients with localized lymphoma can be made.

This proposal should not, however, be construed as an attempt to minimize the interpretation of lymph node morphology, but rather an attempt to diminish the emphasis placed upon description of cytologic differentiation as a basis for treatment-decision when, in fact, flexibility in choice of treatment is remarkably limited. Rather than labor the role of alternative descriptive classifications that invite subjectivity and inter-reviewer variability, present needs might best be met by restricting morphologic subcategorization within classifications to the minimum demonstrating clinical utility, e.g., low grade versus intermediate and high grade. While objective and quantitative measurements reflecting lymphoma cell origin, differentiation, and proliferative state are becoming more readily available, their independent prognostic significance must be addressed through defined prospective, curative, treatment programs if they are to form the basis of a clinically relevant disease classification.

SUMMARY

In an era of increasingly effective chemotherapy for patients with advanced,

intermediate, and high grade lymphoma, the role of radiotherapy for patients with localized disease requires clarification. Based upon a retrospective analysis of patients receiving radical irradiation for localized intermediate and high grade lymphoma between 1967 and 1978, it is proposed that a group of patients with a favorable prognosis (cause-specific survival rate of 87% and recurrence rate of 23% at 10 years) may be defined by the attributes: age, stage, and tumor bulk. Such attributes also define those patients in whom chemotherapy is either essential or may contribute to improvements in relapse rate and survival. While no overall prognostic significance could be attributed to nodal versus extra nodal presentation, some justification for distinguishing mucosa-associated lymphoid tissue lymphoma from lymphomas arising in other extra nodal sites was identified.

The same attributes also permit discrimination of prognostic groups with reference to radiation therapy for patients with localised low grade lymphoma. While the observation period required to establish cure for patients with low grade lymphoma may be decades, the use of radiation therapy can be rationalized given the identification of patients with a highly favorable prognosis with radiation alone, the absence of treatment-related morbidity, and the absence of effective systemic therapy.

Undue emphasis upon cytological differentiation within histologic classification as a basis for treatment discussion may be inappropriate. Sound clinical decisions can be made with access to readily available clinical information and limited descriptive morphology of lymph node lesions. Objective, quantitative techniques for evaluation of lymphoma cells may overcome the subjective difficultities of morphologic classification. Their clinical reference to decision-making must, however, be established by determination of their independent prognostic significance in defined prospective treatment programs.

REFERENCES

1. Schein, P.S., DeVita, V.T., Jr., Hubbard, S.P., et al.: Bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma. *Ann. Intern. Med. 85:*471-22, 1976.
2. Fisher, R.I., DeVita, V.T., Jr., Hubbard, S.M., et. al.: Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of pro MACE and MOPP chemotherapy. *Ann. Intern. Med. 98:*304-09, 1983.
3. Skarin, A.T., Canellos, G.P., Rosenthal, D.S., et al.: Improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high dose methotrexate alternating with standard agents (M-BACOD). *J. Clin. Oncol. 1:*91-98, 1983.
4. Klimo, P. and Connors, J.M.: MACOP-B chemotherapy for the treatment of dif-

fuse large-cell lymphoma. *Ann. Intern. Med. 102:*596-602, 1985.
5. Miller, T.P. and Jones, S.E.: Chemotherapy of localized histiocytic lymphoma. *Lancet 1:*358-60, 1979.
6. Monfardini, S., Banfi, A., Bonadonna, G., et. al.: Improved five-year survival after combined radiotherapy-chemotherapy for Stage I and II non-Hodgkin's lymphomas. *Int. J. Radiat. Oncol. Biol. Phys. 6:*125-34, 1980.
7. Sutcliffe, S.B., Gospodarowicz, M.K., Bush, R.S., et al.: Role of radiation therapy in localized non-Hodgkin's lymphoma. *Radiother. Oncol. 4:*211-23, 1985.
8. Rappaport, H.: Tumors of the Hematopoietic System. In: *Atlas of Tumor Pathology,* Section 3, Fascicle 8. Washington, D.C., U.S. Armed Forces Institute of Pathology, 1966.
9. The non-Hodgkin's Lymphoma Pathologic Classification Project: NCI sponsored study of classification of non-Hodgkin's lymphoma. *Cancer 49:*2112-35, 1982.
10. Gospodarowicz, M.K., Bush, R.S., Brown, T.C., and Chua, T.: Curability of gastrointestinal lymphoma with combined surgery and radiation. *Int. J. Radiat. Oncol. Biol. Phys. 9:*3-9, 1983.
11. Dragosics, B., Bauer, P., and Radaszkiewicz, T.: Primary gastrointestinal non-Hodgkin's lymphomas. *Cancer 55:*1060-73, 1985.
12. Turner, R.R., Colby, T.V., and MacKintosh, F.R.: Testicular lymphomas: A clinicopathologic study of 35 cases. *Cancer 48:*2095-2102, 1981.
13. Berry, M.P. and Simpson, W.J.K.: Radiation therapy in the management of primary malignant lymphoma of the brain. *Int. J. Radiat. Oncol. Biol. Phys. 7:*55-59, 1981.
14. Lang, G.K. Surer, J.L., Green, W.R., et al.: Ocular reticulum cell sarcoma. *Retina 5:*79-86, 1985.
15. Douglas, A.P. and Weetman, A.P.: Lymphocytes and the gut. *Digestion 13:*344-71, 1975.
16. McWilliams, M., Phillips-Quagliata, J.M., and Lamm, M.E.: Characteristics of mesenteric lymph node cells homing to gut-associated lymphoid tissue in syngeneic mice. *J. Immunol. 115:*54-58, 1975.
17. Butcher, E.C., Scollay, R.G., and Weissman, I.L.: Organ specificity of lymphocyte migration: Mediation by highly selective lymphocyte interaction with organ-specific determinants on high endothelial venules. *Eur. J. Immunol. 10:*556-61, 1980.
18. Chabner, B.A., Johnson, R.E., Young, R.C., et al.: Sequential non-surgical and surgical staging of non-Hodgkin's lymphoma. *Ann. Intern. Med. 85:*149-54, 1976.